OFFICE OF NAVAL RESEARCH

Contract N00014-82K-0612

R&T CODE: 4133032

TECHNICAL REPORT NO. 77

Chemical Sensors Based on Ultrathin Film Composite Membranes

by

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Prepared for publication

in

Analytical Chemistry

Department of Chemistry
Colorado State University
Ft. Collins, CO 80523

August 20, 1992

REPORT DOCUMENTATION PAGE

OMB No 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	8/21/ 1992	Interim

4. TITLE AND SUBTITLE
Chemical Sensors Based on Ultrathin Film Composite Membranes

5. FUNDING NUMBERS
Contract
N00014-82K-0612

6. AUTHOR(S)
Barbara Ballarin, Charles J. Brumlik, Del R. Lawson, Wenbin Liang, Leon S. Van Dyke and Charles R. Martin

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8. PERFORMING ORGANIZATION REPORT NUMBER
ONR TECHNICAL REPORT # 77

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
800 North Quincy Street
Arlington, VA 22217

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
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13. ABSTRACT *(Maximum 200 words)*

This paper introduces a new approach for designing chemical sensors. This approach is based on a concept borrowed from the membrane-based separations area - ultrathin film composite membranes. Ultrathin film composite membranes consist of an ultrathin (less than ca. 100 nm-thick) polymer skin coated onto the surface of a microporous support membrane. These composite membranes have made a tremendous impact on the field of membrane-based separations because they can offer high permeate flux without sacrificing chemical selectivity. These two qualifies (high permeate flux and high chemical selectivity) are also required in polymeric barrier layers in chemical sensors. Therefore, the ultrathin film composite membrane concept should be applicable to sensor design. In this paper we present proof of this concept by showing the response characteristics of a prototype glucose sensor based on an ultrathin film composite membrane.

14. SUBJECT TERMS
Sensors, biosensors, glucose sensor, thin polymer films.

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
		UNCLASSIFIED	

CHEMICAL SENSORS BASED ON ULTRATHIN FILM COMPOSITE MEMBRANES

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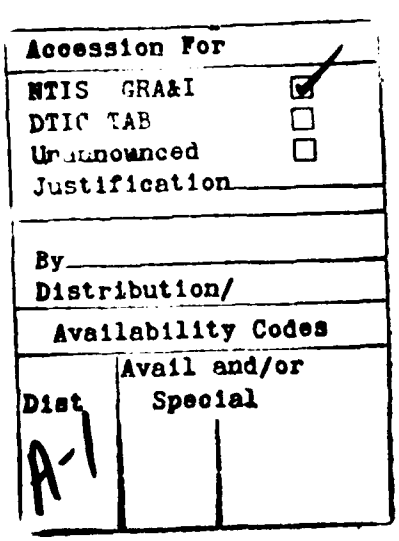
ABSTRACT

This paper introduces a new approach for designing chemical sensors. This approach is based on a concept borrowed from the membrane-based separations area - ultrathin film composite membranes. Ultrathin film composite membranes consist of an ultrathin (less than ca. 100 nm-thick) polymer skin coated onto the surface of a microporous support membrane. These composite membranes have made a tremendous impact on the field of membrane-based separations because they can offer high permeate flux without sacrificing chemical selectivity. These two qualities (high permeate flux and high chemical selectivity) are also required in polymeric barrier layers in chemical sensors. Therefore, the ultrathin film composite membrane concept should be applicable to sensor design. In this paper we present proof of this concept by showing the response characteristics of a prototype glucose sensor based on an ultrathin film composite membrane.

BRIEF

Ultrathin film composite membranes form the basis for a new generic design for chemical sensors.



INTRODUCTION

This paper introduces a new and, we believe, general approach for designing chemical sensors. This approach is based on a concept borrowed from the membrane-based separations area (1) - ultrathin film composite membranes (2-7). Sensors based on such composite membranes should have a number of potential advantages including fast response time, simplicity of construction, and applicability to a number of molecular recognition chemistries and signal transduction schemes. In order to demonstrate the feasibility of this new approach for sensor design, we have prepared and evaluated a prototype electrochemical glucose sensor. This particular sensor was chosen to demonstrated the feasibility of this new sensor-design concept because the molecular recognition and signal transduction chemistries are well established (8-11). A number of other sensing schemes (12-16) could, however, been chosen. Hence, the purpose of this paper is not to describe a new glucose sensor but to provide proof of concept for a new sensor design.

CONCEPTS

The development of ultrathin film composite membranes was one of the most important breakthroughs in the membrane-separations area (2-5). Such composites consist of an ultrathin (less than ca. 100 nm-thickness) chemically-selective "skin" bonded to the surface of a microporous support membrane (3-6). The desired chemical separation occurs within the ultrathin skin and the thinness of this skin insures that the flux of permeate across the membrane is high. The microporous support provides the requisite mechanical strength. Ultrathin film composite membranes can provide high chemical selectivity, high permeate

flux, and good mechanical strength. This combination of properties would be impossible to achieve in a homogeneous membrane (3-5).

In general, barrier layers in sensors must provide some degree of chemical selectivity, yet must also allow for high rates of analyte flux (so as to minimize sensor response time). These membrane requirements (high selectivity and high flux) are identical to the requirements in the membrane separations area (1). Hence, if ultrathin film composites are ideal in this area, these composites should also be ideally-suited for sensor applications.

Two very general types of sensors based on ultrathin thin film composites can be conceptualized. These sensor-types are differentiated by the degree of selectivity required of the composite membrane. The first, and experimentally more difficult, type would be based on a membrane which has molecular specificity for the analyte species. That is, in this type of sensor, molecule-recognition chemistry would be built into the ultrathin film such that only the analyte molecule is extracted and transported by the composite membrane. The second, and experimentally easier, sensor type would be based on an ultrathin film which provides some rudimentary form of selectivity only (i.e. passes small molecules but not large molecules or neutral molecules but not charged molecules, etc.). This "prefilter" membrane would transport the analyte molecules into an internal sensing solution which would contain the molecule recognition chemistry and the transducer for translating this chemistry into a measurable electrical signal.

The prototype glucose sensor described here is an electrochemical example of a "prefilter" membrane device. The internal sensing solution contains glucose oxidase, an electron-transfer mediator (ferrocene-carboxylate, FcC^-), and a working, reference, and

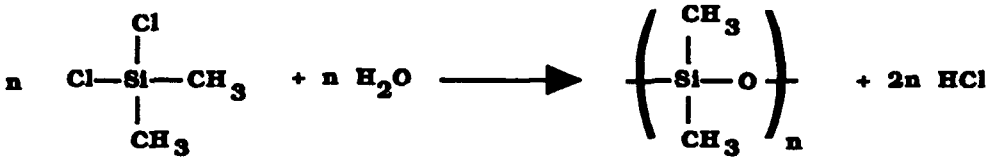
counter electrode (Figure 1). When glucose enters this inner solution (from the analyte solution), it is oxidized by the glucose oxidase; this oxidation process leaves the flavin adenine dinucleotide (FAD) cofactor associated with the enzyme in its reduced state ($FADH_2$) (17). $FADH_2$ is reoxidized by the oxidized form of the mediator; electrochemical reoxidation of the mediator produces an current which is proportional to the concentration of glucose in the analyte solution (8,17). This recognition and transduction chemistry is well known and has been incorporated into other prototype glucose sensors (8,17).

EXPERIMENTAL

Device Fabrication. The support membrane for the ultrathin film composite was an Anopore (Alltech Associates) microporous alumina filter; these membranes contain linear, cylindrical, 250 nm-diameter pores and are ca. 65 % porous (18). One face of the membrane was rendered electronically conductive by sputtering (19,20) an Au film (20-30 nm-thick) across the membrane surface. This Au film served as the working electrode; electrical contact was made by using Ag-epoxy to attach a Cu wire to the Au surface (19) (Figure 1). This Au film is too thin to block the pores at the membrane surface (5,21); this is important because analyte must pass through the membrane into the internal sensing solution (Figure 1).

The surface of the membrane opposite to the Au film was then coated with an ultrathin (ca. 50 nm) skin of a poly(dimethylsiloxane); this was accomplished by using a novel interfacial polymerization method developed in these laboratories (22). Briefly, the alumina support membrane is placed on a wet filter paper, which acts as a source of water vapor. The upper face of the membrane is then exposed to dimethlydichlorosilane vapor.

This causes a thin skin of poly(dimethylsiloxane) to form across the upper surface of the membrane via (22)



Scanning electron micrographs of an Anopore membrane before and after film coating are shown in Figure 2. Note that the film obtained is so thin that the film cross-section (at this contrast range) approaches the resolution limit of this microscope (23). We estimate that these films are on the order of 50 nm in thickness.

We have found that in sensors based on this simple homopolymer, the mediator, FcC^-, leaches from the internal solution into the analyte solution. In order to mitigate this problem, the films were subsequently cross-linked and sulfonated. Cross-linking was accomplished by exposing the film to a 5 % (v/v) solution of trichloromethylsilane, in ethanol. Sulfonation was accomplished by exposing the film to a 2 % (v/v) solution of 2-(4-chlorosulfonylphenyl)ethyltrimethoxy silane, also in ethanol. These silanes attack the ends of the homopolymer chains and thus introduce the desired chemical functionality into the polymer film. The details of these materials science aspects of this sensor will be discussed in a future paper (22).

Finally, the Au/Anopore/polymer composite membrane was glued to the end of a glass tube (I.D. = 0.64 cm), which forms the body of the sensor (Figure 1). The internal solution - a small volume of pH 7.0 phosphate buffer (0.05 M) containing 200 units per mL of glucose oxidase (Sigma; Type VII) and saturated (ca. 3 mM) with FcC^- - was then added. A Ag/AgCl reference and gold wire counter electrode were immersed within this internal solution (Figure 1). As indicated in Figure 1, one of the beauties of this new approach for making sensors is that a totally self-contained sensing device is obtained; i.e. external electrodes are not required.

Response Characteristics of the Prototype Sensor. The response characteristics of these devices were probed using a variety of experiments; the most straight forward was a simple calibration experiment. The sensor was placed in a known volume (30.0 mL) of pH = 7.0 phosphate buffer which initially contained no glucose. The potential of the Au film working electrode was then scanned through the mediator oxidation wave to obtain a cyclic voltammogram for the mediator confined within the internal solution. A typical voltammogram is shown as Curve A in Figure 3. Known volume increments of glucose solution were then added to the external "analyte" solution. The analyte solution was stirred continually. A voltammogram for the mediator was then obtained as before; a typical voltammogram is shown as Curve B in Figure 3. Note that the wave now has a catalytic appearance (9) due to the reaction between the oxidized mediator and $FADH_2$; this electrochemistry has been described in detail by others (11,17,24-26). Calibration curves were obtained by plotting the difference between the peak current in Curve A and the plateau current in Curve B vs. the concentration of glucose in the external solution (Figure 4).

The response time of the device was also investigated. This was accomplished via a potential-step experiment. The sensor was placed in a vigorously-stirred buffer solution that was initially devoid of glucose. The potential of the Au film working electrode was stepped from 0 V (no mediator oxidation) to +0.5 V, where the oxidation of the mediator in the internal solution occurred at the diffusion-controlled rate. (All potentials are reported vs. Ag/AgCl). The resulting current-time transient associated with mediator oxidation was recorded on an X-Y recorder. The potential was then returned to 0 V to re-reduce the mediator. A second (identical) potential step was then conducted. However, in this case, the external (analyte) solution was spiked with glucose 4.5 sec. after initiating the potential step. The current-time transient was again recorded. The response time of the sensor was obtained from the difference between the two transients.

Oxygen present in the analyte solution presents a potential problem for enzyme/mediator-based sensors of this type. This is because O_2 can also oxidize $FADH_2$. Thus, if the O_2 concentration in the analyte solution changes during an analysis, the response of the device to glucose (via the mediator-oxidation route) will also change. Various schemes for circumventing this problem have been devised (10). We expected that our sensors would be less susceptible to changes in O_2 concentration in the analyte phase, because the electrochemistry occurs in the internal solution which is always exposed to air. To test this premise, we obtained voltammograms for the mediator with the sensor in contact with an air-saturated and a degassed analyte solution.

RESULTS AND DISCUSSION

The primary function of the ultrathin film composite membrane in this simple prototype sensor is to confine the internal solution components. This necessitates that the ultrathin polymer film is completely defect-free. We have conducted gas-transport measurements on such thin poly(dimethylsiloxane) films (22); these measurements indicate that these films have no defects. This was also proven, in the present studies, by monitoring the external solution for glucose oxidase.

If defects of the size of the glucose oxidase molecule (160,000 - 186,000 M.W. or ca. 4.3 nm in diameter) (27-29) were present in these films, the enzyme would leak freely into the analyte solution. However, no glucose oxidase could be detected (electrochemically) in the analyte solution, even after overnight exposure of the sensor to this solution. These results show that the ultrathin films used here have no defects which are larger than ca. 4.3 nm. While not evaluated in these preliminary investigations, this lack of transport of proteins should also be useful in keeping proteins that might be present in the analyte solution from entering the internal solution. Hence, the ultrathin film composite membranes used here have a rudimentary *sized-based selectivity*.

Chemical selectivity was also built into these films so as to minimize transport of the FcC^- through the film; this was accomplished by sulfonating and cross-linking the films. While this approach dramatically lowered the rate of FcC^- transport, trace concentrations of FcC^- could be detected (electrochemically) in the analyte solution after several hours of exposure of the sensor to this solution. This problem could be further mitigated, or perhaps eliminated, by increasing the molecular weight and the anionic charge of the mediator.

Alternatively, the film chemistry could be changed. For example, recent work has shown that $FADH_2$ can give its electrons directly to the doped form of polypyrrole; i.e. a mediator is not necessary (30). We have recently developed an interfacial polymerization method to synthesize ultrathin film composite membranes based on polypyrrole and its derivatives (3). This creates the exciting possibility of making a mediator-free glucose sensor of the thin film composite type.

The mediator-based chemistry used here to detect glucose is well know and interference from other molecules, that might be present in the analyte solution, have been studied in detail (10). For this reason (and because the primary object of the work, to date, has been to provide proof of concept for a general sensor design) we have not yet investigated the effects of these interferences on the response of this prototype sensor. It is important to point out, however, that a number of these potential interferents are anionic (10). Because the rates of anion transport in the sulfonated film used here is low (vide supra), this film should provide some level of protection against these anionic interferents.

A calibration curve for glucose is shown in Figure 4. As is typical for enzyme-based sensors of this type, this curve shows a region of linear response at lower concentrations and a region of flattened response at higher concentrations (9,11,17,24-27,31). The reasons for these response characteristics have been discussed by others (9,11,17,24-27). The extent of the linear region can be adjusted by varying the concentration of mediator and glucose oxidase in the internal solution. The calibration curve shown in Figure 4 is linear throughout the physiological concentration range for glucose (4 to 5 mM for healthy patients and up to 20 mM for diabetics) (32,33).

Finally, one of the most important potential advantage of a sensor based on an ultrathin film composite membrane is fast response time. Figure 6 shows that extremely fast response is, indeed, observed with these simple prototype devices. The curve labeled "no glucose" is a current-time transient associated with a potential-step oxidation of the mediator within the internal solution, when the external (analyte) solution is devoid of glucose. A typical chronoamperometric decay of current with time is observed (34). The curve labeled "with glucose" is associated with an analogous potential step; however, in this case, the external solution was spiked with glucose 4.5 sec. after initiating the step. A steady-state signal to glucose is observed in less than two seconds. This is one of the fastest responses of any enzyme-based glucose sensor to be described in the literature to date (11,35-37).

CONCLUSIONS

We have demonstrated a new concept in chemical sensor design - sensors based on ultrathin film composite membranes. We believe that this design is generic in that it should be amenable to other molecular recognition schemes (38), other film chemistries (3-5,7), and other signal transduction processes (12-16). With regard to other film chemistries, we have developed four new interfacially polymerization methods for forming ultrathin film composite membranes (3-5,7). With these methods, films based on almost any conceivable chemistry could be fabricated for sensors of this type. Alternative transduction schemes might include fiber optic-based transducers (12- 16). For example, the molecular-recognition chemistry might produce a colored species which could be monitored by a fiber optic probe inserted into the internal sensing solution (16,39,40).

Furthermore, because the internal solution and transduction system can be easily removed from the body of the device (Figure 1), this sensor design creates the interesting prospect of using a single sensor body to make a variety of specific sensors. This design also allows for replenishing and sampling of the internal solution. This capability could be built into the device by adding solution inlet and outlet lines. The internal solution could also be subjected to additional chemical analyses to detect species which partitioned through the membrane. In this sense, the sensor would resemble a microdialysis device (41,42). Finally, sensors based on thin film composites should also be easy to miniaturize. One approach might be to coat the thin film onto a microporous hollow fiber. As part of our membrane separation work we are developing methods to coat such hollow fibers with ultrathin polymer films (43). We believe that the ultrathin film composite membrane is a promising and versatile approach for sensor design.

ACKNOWLEDGEMENTS

This work was supported by the Office of Naval Research and the Air Force Office of Scientific Research. Barbara Ballarin was supported by the Ministero Dell'Universita' e Della Ricerca Scientifica e Tecnologica (Rome).

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LIST OF FIGURES

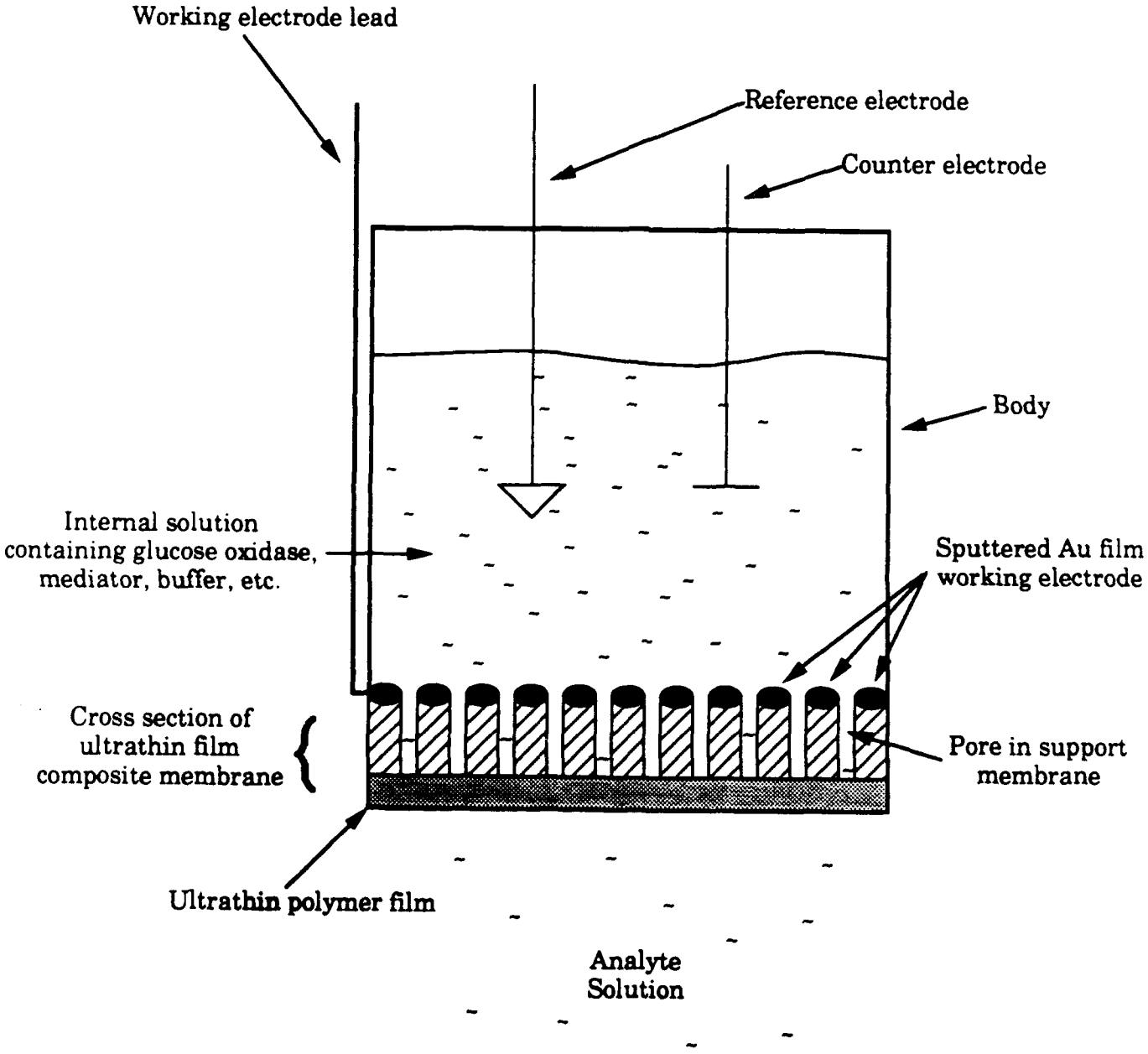

Working electrode lead
Reference electrode
Counter electrode
Body
Internal solution containing glucose oxidase, mediator, buffer, etc.
Sputtered Au film working electrode
Cross section of ultrathin film composite membrane
Pore in support membrane
Ultrathin polymer film
Analyte Solution

Fig. 1

Scanning electron micrographs of Anopore membrane before and after polymerization.

Fig 2

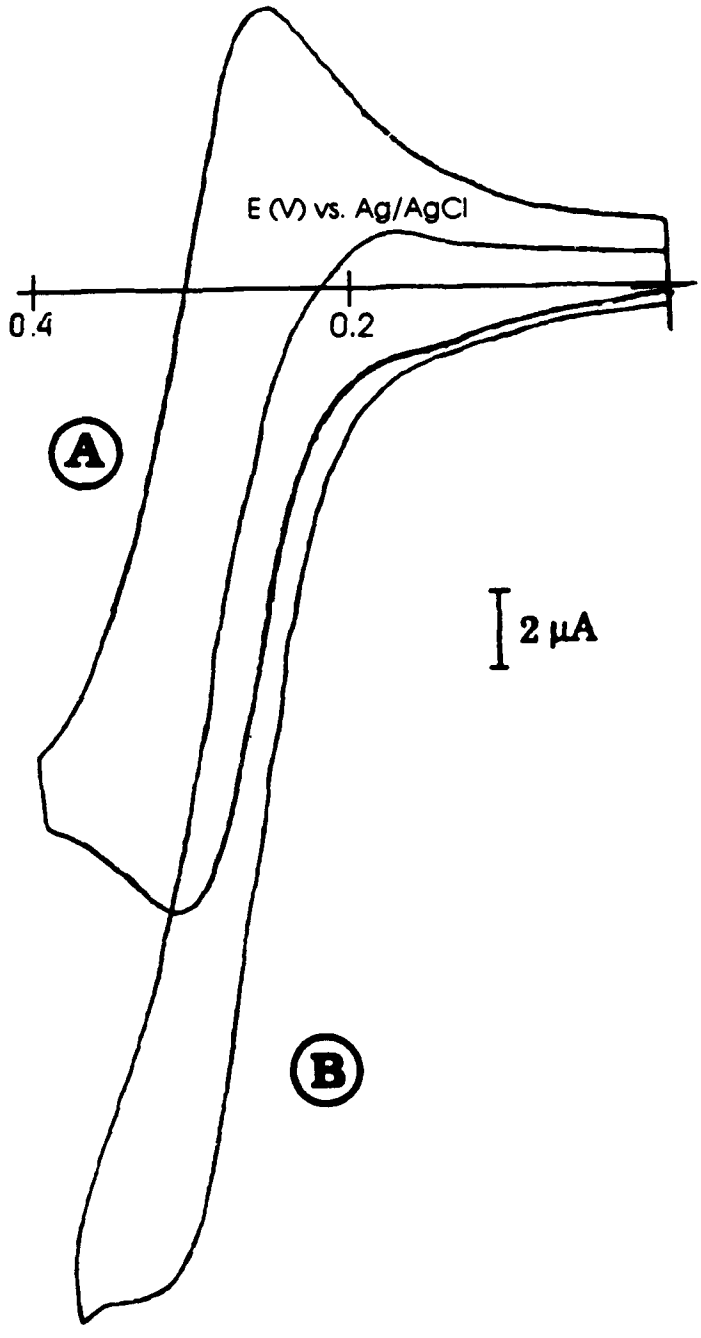
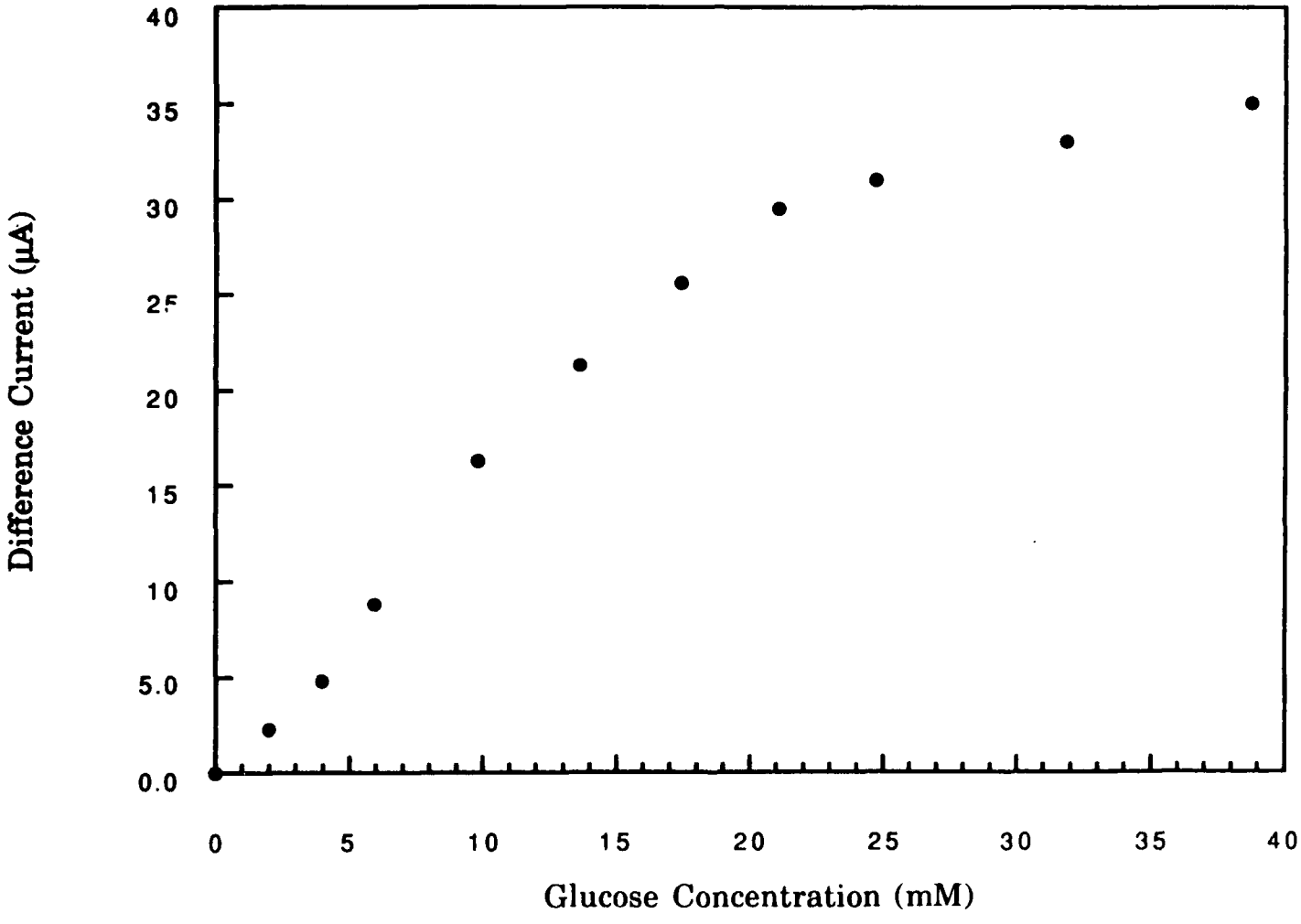


Figure 3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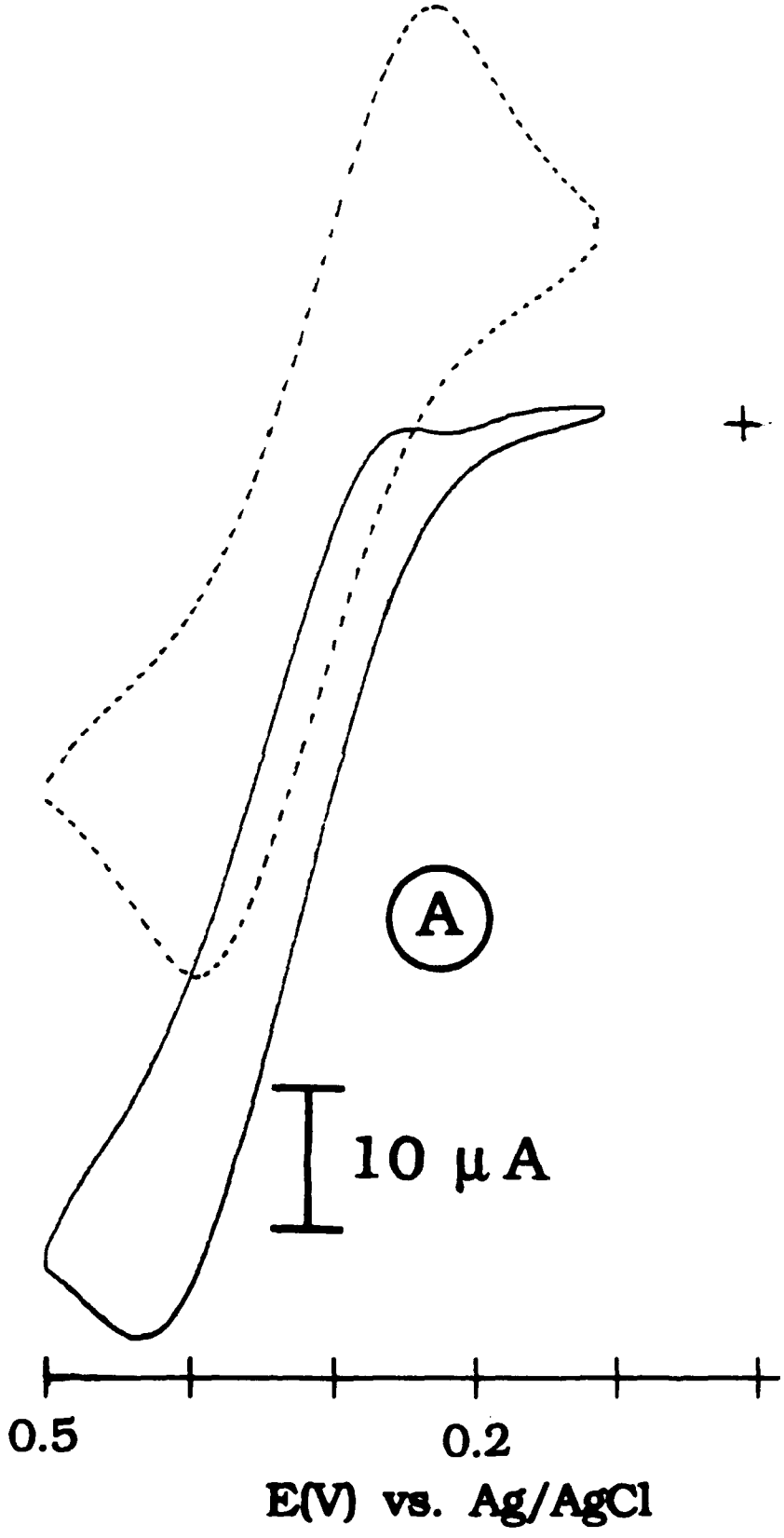
Glucose Concentration (mM)

Fig 9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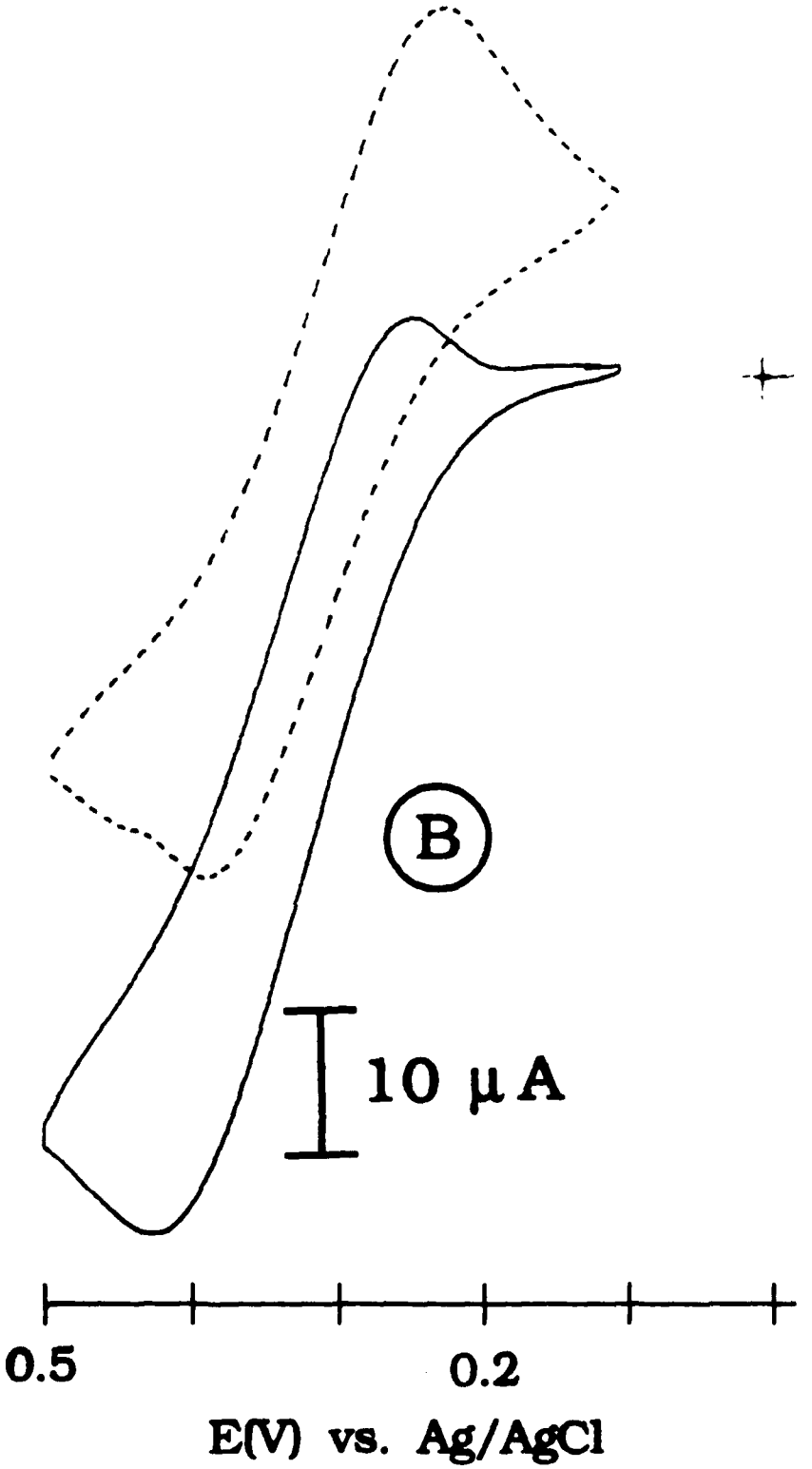
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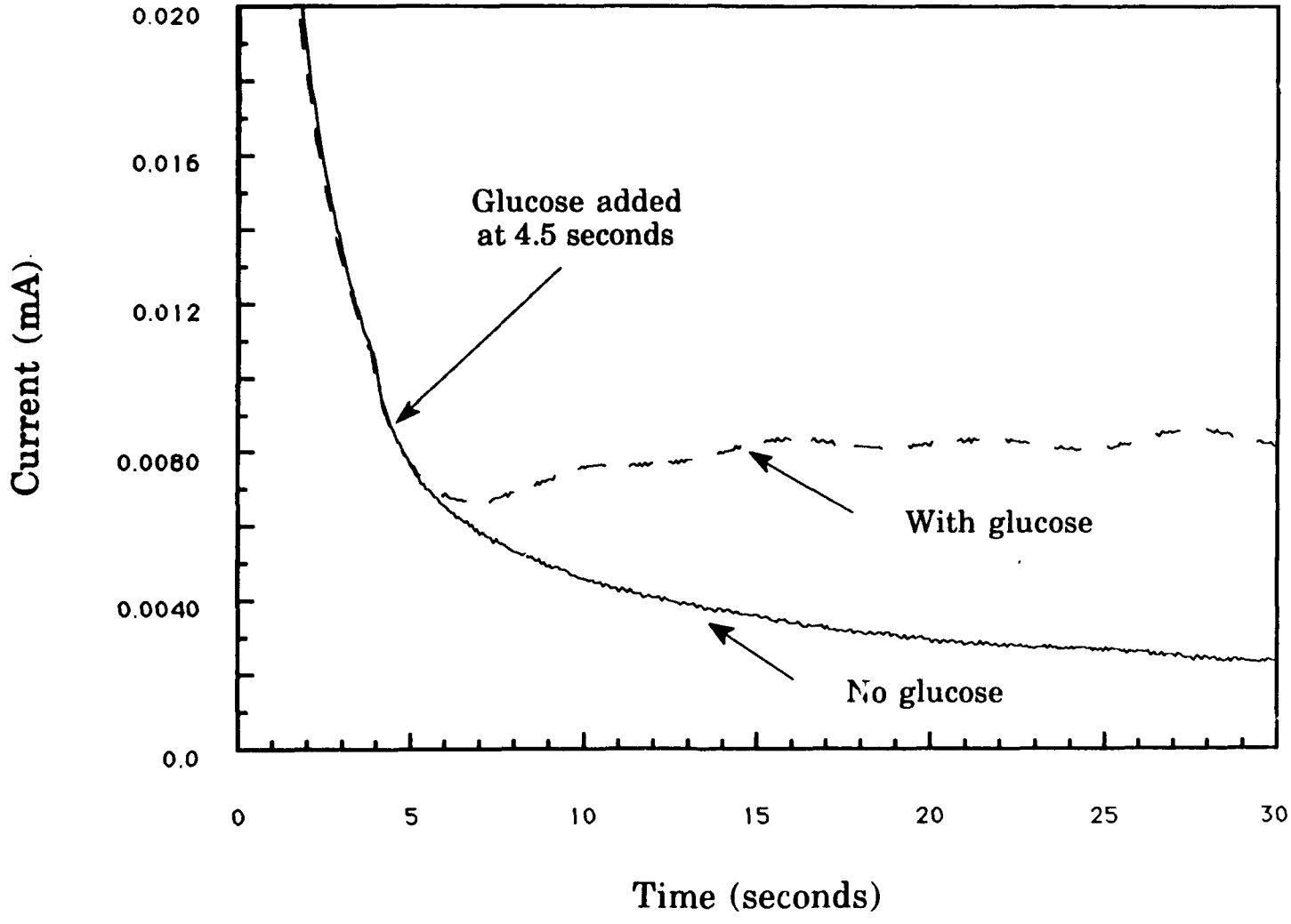
E(V) vs. Ag/AgCl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